The Cost-Effectiveness of Lifestyle Modification or Metformin in Preventing Type 2 Diabetes in Adults with Impaired Glucose Tolerance

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Background: **The Diabetes Prevention Program (DPP) demonstrated that interventions can delay or prevent the development of type 2 diabetes.**

Objective: **To estimate the lifetime cost–utility of the DPP interventions.**

Design: **Markov simulation model to estimate progression of disease, costs, and quality of life.**

Data Sources: **The DPP and published reports.**

Target Population: **Members of the DPP cohort 25 years of age or older with impaired glucose tolerance.**

Time Horizon: **Lifetime.**

Perspectives: **Health system and societal.**

Interventions: **Intensive lifestyle, metformin, and placebo interventions as implemented in the DPP.**

Outcome Measures: **Cumulative incidence of diabetes, microvascular and neuropathic complications, cardiovascular complications, survival, direct medical and direct nonmedical costs, quality-adjusted life-years (QALYs), and cost per QALY.**

Results of Base-Case Analysis: **Compared with the placebo intervention, the lifestyle and metformin interventions were estimated to delay the development of type 2 diabetes by 11 and 3 years, respectively, and to reduce the absolute incidence of diabetes by 20% and 8%, respectively. The cumulative incidence of microvascular, neuropathic, and cardiovascular complications were reduced and survival was improved by 0.5 and 0.2 years. Compared with the placebo intervention, the cost per QALY was approximately $1100 for the lifestyle intervention and $31 300 for the metformin intervention. From a societal perspective, the interventions cost approximately $8800 and $29 900 per QALY, respectively. From both perspectives, the lifestyle intervention dominated the metformin intervention.**

Results of Sensitivity Analysis: **Cost-effectiveness improved when the interventions were implemented as they might be in routine clinical practice. The lifestyle intervention was cost-effective in all age groups. The metformin intervention did not represent good use of resources for persons older than 65 years of age.**

Limitations: **Simulation results depend on the accuracy of the underlying assumptions, including participant adherence.**

Conclusions: **Health policy should promote diabetes prevention in high-risk individuals.**

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*The members of the Diabetes Prevention Program Group are listed in Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403. [PMID: 11832527].

During the past half century, the number of persons with diagnosed diabetes in the United States has increased 4- to 6-fold (1). Recent large clinical trials from Asia, Europe, and North America have demonstrated that behavioral and medication interventions can delay or prevent the development of type 2 diabetes in persons with impaired glucose tolerance, which is defined by a plasma glucose level between 7.77 mmol/L (140 mg/dL) and 11.04 mmol/L (199 mg/dL) 2 hours after a 75-g oral glucose load (2–6). The Diabetes Prevention Program (DPP) randomly assigned 3234 nondiabetic persons 25 years of age or older with impaired glucose tolerance and fasting glucose levels between 5.27 mmol/L (95 mg/dL) and 6.94 mmol/L (125 mg/dL) to placebo; a lifestyle-modification program with the goals of at least a 7% weight loss and 150 minutes of physical activity per week; or metformin, 850 mg twice daily (4). The mean age of participants was 51 years, and the mean body mass index was 34.0 kg/m^2; 68% were women and 45% were members of minority groups (4). The average follow-up was 2.8 years. Compared with the placebo intervention, the lifestyle intervention reduced the incidence of type 2 diabetes by 58% and the metformin intervention reduced the incidence of type 2 diabetes by 31% (4). We have previously described the costs of the DPP interventions and their cost-effectiveness within the 3-year trial period (7, 8). In this analysis, we project the costs, health outcomes, and cost-effectiveness of the DPP lifestyle and metformin interventions over a lifetime relative to the placebo intervention.

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Context

The Diabetes Prevention Program (DPP) showed that lifestyle changes or metformin effectively decreased the development of type 2 diabetes in adults with impaired glucose tolerance. The economics of these interventions is important to policymakers.

Contribution

This cost-effectiveness model estimates that the DPP lifestyle intervention would cost society about $8800 and metformin would cost about $29 900 per quality-adjusted life-year saved. While lifestyle intervention had a favorable cost-effectiveness profile at any adult age, metformin was not cost-effective after age 65 years.

Implications

The cost-effectiveness of lifestyle intervention to prevent type 2 diabetes in high-risk individuals is within the range that American society typically finds acceptable for health care interventions.

–The Editors

METHODS

Clinical Trial

The lifestyle intervention involved a healthy, low-calorie, low-fat diet and moderate physical activity, such as brisk walking. The lifestyle intervention was implemented with a 16-lesson core curriculum covering diet, exercise, and behavior modification that was taught by case managers on a one-on-one basis, followed by individual sessions (usually monthly) and group sessions with case managers (9). At the end of the study, 38% of participants in the lifestyle intervention group had lost at least 7% of their initial body weight. The metformin and placebo interventions were initiated at a dosage of 850 mg once a day. At 1 month, the dosage of metformin or placebo was increased to 850 mg twice daily. Case managers reinforced adherence during individual quarterly sessions (10). At the end of the study, 72% of participants in the metformin intervention group and 77% of participants in the placebo intervention group took at least 80% of the prescribed dose. All participants received standard lifestyle recommendations through written information and an annual 20- to 30-minute individual session that emphasized the importance of a healthy lifestyle (10).

Simulation Model

We assessed the progression from impaired glucose tolerance to onset of diabetes to clinically diagnosed diabetes to diabetes with complications and death by using a lifetime simulation model originally developed by the Centers for Disease Control and Prevention and Research Triangle Institute International. The model has a Markov structure and includes annual transition probabilities between disease states (11). In addition to disease progression, the model tracks costs and quality-adjusted life-years (QALYs). The model has been described elsewhere (11). For our analyses, we modified the model to include data from the DPP on progression, costs, and quality of life associated with impaired glucose tolerance, data from the United Kingdom Prospective Diabetes Study (UKPDS) on diabetes progression and complications, and new data on cost and quality of life associated with diabetes. A technical report (available at www.annals.org) describing the model is available.

Disease Progression, Complications, and Comorbid Conditions

Impaired Glucose Tolerance to Onset of Type 2 Diabetes

We analyzed data from the DPP to assess the annual hazard of diabetes onset in the lifestyle, metformin, and placebo intervention groups. For patients receiving the placebo intervention, the annual hazard of diabetes onset was 10.8 per 100 person-years. At 3 years of follow-up, the risk reductions for the lifestyle and metformin interventions were 55.8% and 29.9%, respectively. In the base-case analysis, we assumed that the lifestyle and metformin interventions would be applied until diabetes onset and that the health and quality-of-life benefits associated with the interventions persisted until diabetes onset.

Complications and Comorbid Conditions Associated with Impaired Glucose Tolerance

We analyzed data from the DPP and other published sources to assess the prevalence of complications and comorbid conditions in participants with impaired glucose tolerance. At baseline, 6.0% of DPP participants had microalbuminuria and 0.4% had nephropathy. The DPP did not measure peripheral neuropathy, but previous studies found that the prevalence of neuropathy in persons with impaired glucose tolerance was 74% of that in persons with newly diagnosed type 2 diabetes (12) and 12.3% of persons with newly diagnosed type 2 diabetes have neuropathy (13). Therefore, we assumed that at baseline, 8.5% of DPP participants had clinical neuropathy. At baseline, 28% of DPP participants had hypertension, 45% had dyslipidemia, 7% were smokers, 1.1% had a history of cerebrovascular disease, and 2.0% had a history of myocardial infarction. No other complications were present.

We assumed that during impaired glucose tolerance, microvascular or neuropathic complications would not progress. We assumed that hypertension and dyslipidemia developed at the rates observed in the DPP. On the basis of 2 large studies (14, 15), we assumed that the incidences of coronary heart disease and cerebrovascular disease in patients with impaired glucose tolerance were 58% and 56%, respectively, of those observed in patients with type 2 diabetes. We further assumed that non–diabetes-related mortality for persons with impaired glucose tolerance was the same as for persons with diabetes (16).

Table 1. **Total Direct Medical Costs and Health Utility Scores of Impaired Glucose Tolerance***

Variable	Lifestyle Intervention		Metformin Intervention		Placebo Intervention	
	Men	Women	Men	Women	Men	Women
Costs per treatment year, $						
First year	2600	2800	2400	2500	1400	1600
Second year	1900	2100	2200	2200	1300	1600
Third and subsequent years	1900	2100	2100	2200	1300	1600
Health utility score	0.72	0.68	0.70	0.66	0.70	0.66

* Costs include direct medical costs of the Diabetes Prevention Program interventions and direct medical costs of care outside the Diabetes Prevention Program.

Onset of Type 2 Diabetes to Clinical Diagnosis of Type 2 Diabetes

In the DPP, participants were tested for diabetes every 6 months; diabetes was diagnosed at onset. In routine clinical practice, type 2 diabetes is estimated to develop 8 to 12 years before its clinical diagnosis (17, 18). In our base-case analysis, we therefore assumed that a 10-year delay occurred between the onset and clinical diagnosis of diabetes.

Participants in the DPP had a mean hemoglobin A_{1c} level of 6.4% at the onset of diabetes. Participants in the UKPDS had a mean hemoglobin A_{1c} of 7.1% after a dietary run-in period but before randomization (13). Both DPP placebo participants and UKPDS participants received standard lifestyle recommendations. Accordingly, we assumed that during the 10-year interval between onset and clinical diagnosis of diabetes, patients were treated for type 2 diabetes and that hemoglobin A_{1c} level increased at 0.07% per year from 6.4% to 7.1%.

Complications and Comorbid Conditions Associated with Undiagnosed Diabetes

We further assumed that between onset and clinical diagnosis of diabetes, microvascular and neuropathic complications progressed slowly, such that by clinical diagnosis of type 2 diabetes, their prevalence reached the level observed in the UKPDS cohort at randomization (13, 19, 20). We assumed that blood pressure and lipid levels progressed as they did in DPP participants and that cardiovascular complications occurred as they would in type 2 diabetes according to risk factors and hemglobin A_{1c} level (21, 22).

Clinical Diagnosis of Type 2 Diabetes to Diabetes with Complications and Death

We assumed that after clinical diagnosis, all persons with type 2 diabetes received intensive glycemic management as described in the UKPDS (13). We modeled changes in hemoglobin A_{1c} and diabetes treatments to reflect those observed in the UKPDS intensive therapy group. We based risk for retinopathy progression on UKPDS 38 (23), risk for nephropathy progression on UKPDS 64 (20), and risk for neuropathy progression on UKPDS 33 (13). We based risk for cerebrovascular disease on UKPDS 60 (22) and risk for coronary heart disease on UKPDS 56 (21).

Costs

Costs of Impaired Glucose Tolerance

To estimate the total direct medical costs of impaired glucose tolerance, we considered the costs of the DPP interventions (the cost of identifying participants, implementing and maintaining the interventions, and monitoring and treating the side effects of the interventions) and the costs of the medical care outside the DPP (7). In analyses from the perspective of society, we included both direct medical costs and direct nonmedical costs. We did not include indirect costs because they are captured in the assessment of QALYs (24).

Table 1 shows the total direct medical costs by treatment group, sex, and year in the DPP (7). Costs were higher in the lifestyle and metformin interventions than in the placebo intervention and higher in women than in men. Costs decreased over time in all 3 intervention groups but after year 1 tended to decrease more in the lifestyle than the metformin intervention group.

To estimate the future costs of impaired glucose tolerance, we constructed a multiplicative cost model with the same structure as that for diabetes. We used the cost of the interventions from the DPP. We used the costs of medical care outside the DPP as baseline and applied the multipliers from the model to account for the incremental costs associated with incident hypertension and cardiovascular disease.

Costs of Type 2 Diabetes

To estimate the costs of type 2 diabetes, we applied a multiplicative prediction model that estimates annual direct medical costs according to demographic characteristics, diabetes treatment, cardiovascular risk factors, and microvascular and macrovascular complications (25). **Table 2** shows the annual direct medical costs of type 2 diabetes. The baseline cost of $1684 is the annual direct medical cost for a nonobese white man with type 2 diabetes who is treated with diet and exercise and has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications (25). If a participant has any characteristic or complication listed in **Table 2**, the annual direct medical cost is then estimated as the product of the baseline cost and the multipliers corresponding to each participant's characteristics or complications.

Table 2. **Annual Direct Medical Costs and Health Utility Scores of Type 2 Diabetes***

Variable	Multiplier (Baseline Cost, $1684†)	Penalty Score (Baseline Health Utility Score, 0.689‡)
Women	1.25	−0.038
Age	§	§
African-American ethnicity	0.82	§
Duration		
Every year after onset	§	§
Body mass index		
Every unit over 30 kg/m^2	1.01	§
Obese	§	−0.021
Diabetes intervention		
Oral antidiabetic agents	1.10	−0.023
Insulin	1.59	−0.034
High blood pressure	1.24	−0.011
Retinopathy		
Nonproliferative retinopathy	§	§
Proliferative retinopathy	§	§
Macular edema	§	§
Blindness in 1 eye	§	−0.043
Blindness in 2 eyes	§	−0.170
Nephropathy		
Microalbuminuria	1.17	§
Proteinuria	1.30	−0.011
Renal failure with dialysis	10.53	−0.078
Neuropathy		
Clinical neuropathy	§	−0.065
History of amputation	§	−0.105
Tingling and burning	§	−0.060
Sores	§	−0.099
Cardiovascular disease		
Angina	1.73	§
History of myocardial infarction	1.90	§
Congestive heart failure	§	−0.052
Stroke		
Transient ischemic attack or stroke	§	−0.044
Stroke with residual	1.30	−0.072

* Annual direct medical cost is the baseline cost ($1684) multiplied by the multipliers for the combination of characteristics, treatments, and complications. For each variable, only the multiplier associated with most severe level should be used. Health utility score is the baseline health utility score minus the penalty scores for the combination of characteristics, treatments, and complications. For each variable, only the penalty score associated with the most severe level should be used. Adapted from references 25 and 26 with permission from the American Diabetes Association.

† The baseline cost represents the median annual direct medical cost for a diet-controlled white man with type 2 diabetes, body mass index of 30 kg/m^2, and without microvascular, neuropathic, or cardiovascular risk factors or complications.

‡ The baseline health utility represents the mean health utility score for a diet-controlled white man with type 2 diabetes, body mass index of 30 kg/m^2, and without microvascular, neuropathic, or cardiovascular risk factors or complications.

§ Variables did not enter into the model.

Combining the data from **Tables 1** and **2**, the approximate annual direct medical costs for a man progressing from impaired glucose tolerance to diabetes with complications would be as follows: impaired glucose tolerance treated with placebo, $1400; diabetes treated with diet and exercise, $1684; diabetes treated with an oral agent, $1900; diabetes treated with an oral agent and complicated by microalbuminuria, $2200; and diabetes treated with an oral agent and complicated by microalbuminuria and high blood pressure, $2700.

Health Utilities

Health utility scores are a measure of health-related quality of life, in which optimal health is assigned a value of 1.0 and the worst health, judged equivalent to death, is assigned a value of 0.0. In economic analysis, the quality adjustment weight for each health state is multiplied by the time in the state and then summed to calculate the number of QALYs (24).

Health Utilities Associated with Impaired Glucose Tolerance

We assessed the health utility scores associated with impaired glucose tolerance by using the self-administered Quality of Well-Being Index, a widely used multiattribute utility model (8). The instrument was administered to DPP participants annually. **Table 1** shows the health utility scores of DPP participants with impaired glucose tolerance by treatment group and sex. In general, health utility scores were higher in the lifestyle intervention group than in the metformin or placebo intervention groups and higher in men than in women.

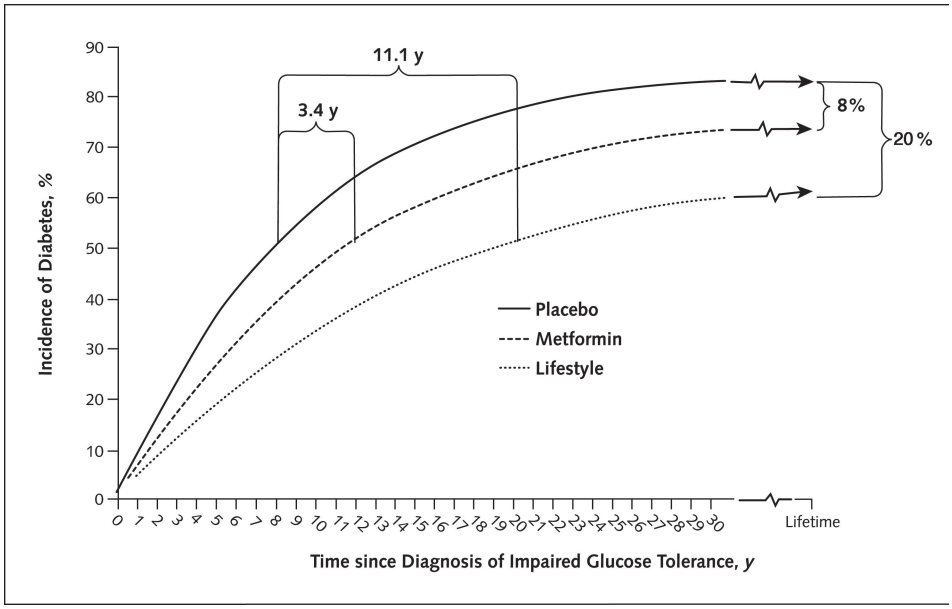
To estimate health utility scores associated with impaired glucose tolerance beyond the 3-year timeframe of the DPP, we constructed an additive health utility model with the same structure as that for diabetes. We used the health utility scores at 3 years as baseline and applied the penalty scores from the model to account for the decreased quality of life associated with hypertension and cardiovascular disease.

Health Utilities Associated with Type 2 Diabetes

To estimate health utility scores associated with type 2 diabetes, we applied an additive prediction model to estimate health utility scores according to demographic, treatment, and disease state variables (26). **Table 2** shows the health utility scores in type 2 diabetes. The baseline health utility score of 0.69 is the health utility score for a nonobese man with type 2 diabetes who is treated with diet and exercise and who has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications. The penalty scores represent the decrement in the health utility score associated with treatments, cardiovascular risk factors, and complications.

Combining the data from **Tables 1** and **2**, the health utility scores for a man progressing from impaired glucose tolerance to diabetes with complications can be described as follows: impaired glucose tolerance treated with placebo, 0.70; diabetes treated with diet and exercise, 0.69; diabetes treated with diet and exercise and complicated by neurop-

Figure. **Simulated cumulative incidence of diabetes among adults with impaired glucose tolerance by the Diabetes Prevention Program treatment group.**



athy, 0.62; and diabetes treated with diet and exercise and complicated by neuropathy, high blood pressure, and stroke, 0.54.

Base-Case Analysis

In each analysis, we used the simulation model to assess disease progression, costs, and QALYs for the entire DPP cohort by age, sex, and race or ethnicity. In the base-case analysis, we modeled the interventions as they were implemented in the DPP and projected year 3 DPP intervention costs, health utility scores, and intervention effectiveness into the future. We assessed the simulated cumulative incidence of diabetes, microvascular and macrovascular complications, and life expectancy. We then assessed simulated lifetime costs and QALYs and the incremental costs and QALYs of the lifestyle and metformin interventions relative to the placebo intervention. We calculated cost-effectiveness ratios by dividing incremental costs by incremental QALYs. In these analyses, we adopted a health system perspective that considered only direct medical costs and discounted both costs and QALYs at 3% per year. Clinical outcomes were not discounted. We expressed costs in U.S. dollars (year 2000).

Sensitivity Analyses

In sensitivity analyses, we first modeled the interventions by age group. We then modeled the interventions as they might be implemented in routine clinical practice and assessed the effect of reducing the costs by modifiying the lifestyle and metformin interventions. Specifically, we recalculated the cost of the lifestyle intervention, assuming that the core curriculum, supervised activity sessions, and lifestyle group sessions were administered as a closed group of 10 participants and that costs were reduced accordingly (8). Studies have shown that group intervention programs are at least as effective as individual programs (27, 28). Similarly, we recalculated the cost of the metformin intervention by using generic metformin priced at 25% the cost of Glucophage (Bristol-Myers Squibb, Princeton, New Jersey). Third, we evaluated the effect of future participant adherence by reducing the effectiveness of the lifestyle and metformin interventions by 20% and 50%, respectively, after year 3. Fourth, we evaluated the effect of both reduced costs (as would be observed with a group lifestyle intervention and a metformin intervention using generic metformin) with reduced effectiveness (a 20% and 50% reduction of the effectiveness of both the lifestyle and metformin interventions, respectively) on lifetime cost-effectiveness. Fifth, we evaluated the effect of lower and higher discount rates. Sixth, to assess cost–utility from a societal perspective, we included the direct nonmedical costs of the interventions (costs of participant time, exercise classes, exercise equipment, food and food preparation items, and transportation) (24). We performed additional sensitivity analyses to assess the effect of variation in the hazard of diabetes and in the delay from onset to diagnosis of diabetes.

We also conducted a probabilistic sensitivity analysis for 50-year-old participants, for which 81 model parameters were simultaneously varied over probability distributions based on published 95% CIs or normal or logistic normal distributions (Appendix and **Appendix Tables 1** to 7, available at www.annals.org) (29). We also applied uniform and triangular distributions where appropriate. We generated parameter values from the distributions by using @Risk software (Palisade Corp., Newfield, New York). We computed the cost-effectiveness of the lifestyle and met-

formin interventions for each of 500 iterations and examined the distribution of cost-effectiveness ratios across iterations.

Role of the Funding Sources

This study was supported by the Diabetes Prevention Program, National Institutes of Health, through the National Institute of Diabetes and Digestive and Kidney Diseases, Office of Research on Minority Health, National Institute of Child Health and Human Development, and National Institute on Aging; Centers for Disease Control and Prevention; Indian Health Service; General Clinical Research Program; National Center for Research Resources; American Diabetes Association; Bristol-Myers Squibb; and Parke-Davis. Corporate sponsors had no role in the design, conduct, or reporting of this analysis or in the decision to submit this manuscript for publication. The Centers for Disease Control and Prevention was involved in the design, conduct, and reporting of the analysis.

RESULTS

Base-Case Analysis

In the base-case analysis, we asked: What are the simulated lifetime costs and health consequences of identifying persons with impaired glucose tolerance and intervening with a lifestyle, metformin, or placebo intervention until they develop type 2 diabetes and intervening with a program of intensive glycemic management after clinical diagnosis?

The **Figure** illustrates the simulated lifetime cumulative incidence of type 2 diabetes by DPP intervention. If the entire DPP cohort were treated with the placebo intervention, approximately 50% of individuals would develop diabetes within 7 years. In contrast, it would take approximately 18 years for 50% of lifestyle-treated participants to develop diabetes and 10 years for 50% of metformin-treated participants to develop diabetes. Thus, compared with the placebo intervention, the lifestyle intervention delays the onset of diabetes by 11 years and metformin delays the onset of diabetes by 3 years. Over a lifetime, 83% of participants treated with the placebo intervention would develop diabetes, as compared with 63% of those treated with the lifestyle intervention and 75% of those treated with the metformin intervention. Thus, compared with the placebo intervention, the lifestyle intervention reduces the absolute risk for developing diabetes by 20% and the metformin intervention reduces the risk for developing diabetes by 8%. The relative risk reductions are 24% and 10%, respectively.

Table 3. **Lifetime Impaired Glucose Tolerance Intervention: Simulated Clinical Outcomes in the Diabetes Prevention Program Cohort***

Outcome	Lifestyle Intervention	Metformin Intervention	Placebo Intervention
Diabetes, %	62.6	74.9	82.8
Life expectancy, *y*	24.7	24.3	24.1
Blindness, %	3.4	4.7	5.6
Nephropathy, %	3.7	4.7	5.5
Renal failure, %	0.6	0.8	1.0
Neuropathy, %	23.1	27.0	30.1
Amputation, %	1.3	1.6	1.9
Stroke, %	19.3	20.6	21.3
Coronary heart disease, %	38.9	41.3	42.1

* Undiscounted.

Table 3 summarizes the simulated lifetime cumulative incidence of diabetes and microvascular and macrovascular complications and life expectancy. These results represent averages for the entire DPP cohort. Individual predictions depend on patient characteristics such as age. In general, health outcomes were best for the lifestyle intervention, intermediate for the metformin intervention, and worst for the placebo intervention. We estimate that the lifestyle intervention increases life expectancy by 0.5 year and reduces the cumulative incidence of blindness by 39%, end-stage renal disease by 38%, amputation by 35%, stroke by 9%, and coronary heart disease by 8%. The metformin intervention increases life expectancy by 0.2 year and reduces the cumulative incidence of blindness by 16%, end-stage renal disease by 17%, amputation by 16%, stroke by 3%, and coronary heart disease by 2%.

Table 4 summarizes the simulated economic outcomes. Over a lifetime, the placebo intervention was associated with the lowest direct medical costs and the lifestyle intervention was associated with the most QALYs. Compared with the placebo intervention, the lifestyle intervention costs $635 more over a lifetime and produces a gain of 0.57 QALY. The cost per QALY (Δ cost/Δ QALY) is approximately $1100. Compared with the placebo intervention, the metformin intervention costs $3922 more over a lifetime and results in a gain of 0.13 QALY. Thus, compared with the placebo intervention, the metformin intervention costs approximately $31 300 per QALY. Compared with the metformin intervention, the lifestyle intervention costs $3287 less over a lifetime and results in a gain of 0.45 QALY. Thus, the lifestyle intervention dominates the metformin intervention.

Sensitivity Analyses

We used sensitivity analyses to assess the effect of age and plausible changes in costs and treatment effectiveness on cost-effectiveness (**Table 5**). Compared with the placebo intervention, the lifestyle intervention was cost-saving in participants younger than 45 years of age and cost-effective in all age groups. In contrast, the metformin intervention was relatively cost-effective in the younger age groups but cost more than $100 000 per QALY in participants 65 years of age or older. The reduced benefit (Δ QALYs) of the metformin intervention in the older age groups may explain the dramatic increase in the incremental cost-effectiveness ratios with age.

If implementing the intervention in a closed group of 10 patients reduced the costs of the lifestyle intervention and the use of generic metformin reduced the cost of the

Table 4. **Lifetime Impaired Glucose Tolerance Intervention: Simulated Economic Outcomes in the Diabetes Prevention Program Cohort***

Outcome	Lifestyle Intervention	Metformin Intervention	Placebo Intervention
Lifetime intervention costs, $	9718	8801	2907
Lifetime outcome costs, $	42 256	46 460	48 432
Total lifetime direct medical costs, $	51 974	55 261	51 339
Lifetime QALYs	10.89	10.45	10.32
Δ Cost vs. placebo, $	635	3922	–
Δ QALY vs. placebo	0.57	0.13	–
Δ Cost/Δ QALY, $	1124	31 286	–

* Costs and QALYs discounted at 3% per year. QALY = quality-adjusted life-year.

metformin intervention, the lifestyle intervention would be cost-saving relative to the placebo intervention and the metformin intervention would cost approximately $1800 per QALY. If future adherence were less than that observed in the DPP and the effectiveness of the lifestyle and metformin interventions were 20% or even 50% less than that observed in the DPP, the lifestyle intervention would cost $3100 to $7900 per QALY compared with the placebo intervention and the metformin intervention would cost $38 000 to $52 600 per QALY. If both the lifestyle and metformin interventions were implemented at lower costs, reflecting group lifestyle classes and generic metformin pricing but with effectiveness reduced by 20% or 50% relative to that observed in the DPP, the lifestyle intervention would be cost-saving relative to the placebo intervention and the metformin intervention would cost approximately $6600 to $21 000 per QALY. Reducing or increasing the discount rate reduces or increases the cost per QALY. When a societal perspective is adopted and direct nonmedical costs are included, the lifetime costs of the lifestyle intervention increase by more than $4300 and the cost-effectiveness ratio increases to approximately $8800 per QALY. Adopting a societal perspective has little effect on the cost-effectiveness of the metformin intervention. Similarly, using the lower and upper bounds of 95% CIs for the hazard of diabetes and varying the duration of undiagnosed diabetes from 5 to 15 years had little effect on the cost-effectiveness of the lifestyle or metformin interventions (data not shown).

The probabilistic sensitivity analyses revealed that among participants 50 years of age, the median cost of the lifestyle intervention was $4137 per QALY (95% of the cost-effectiveness ratios were between −$587 and $9456 per QALY). The median cost of the metformin intervention was $36 327 per QALY (95% of the cost-effectiveness ratios were between $16 509 and $84 583 per QALY).

DISCUSSION

We previously demonstrated that the DPP lifestyle and metformin interventions were more expensive than placebo intervention (7). Yet, delaying or preventing type 2 diabetes delays or prevents the direct medical costs of diabetes, including the costs of diabetes education and nutritional counseling, glucose monitoring, treatment, surveillance for complications, and treatment of complications. It also improves quality of life and length of life. We recently demonstrated that from the perspective of a health system over 3 years and relative to the placebo intervention, the lifestyle and metformin interventions cost $16 000 and $31 000 per case of diabetes prevented and $32 000 and $100 000 per QALY, respectively (8). Adopting a 3-year time horizon overestimates treatment costs and underestimates the benefits of the lifestyle and metformin interventions (8). In this paper, we aimed to extend the results of our previous analyses and project the costs, health outcomes, and cost-effectiveness of the lifestyle and metformin

Table 5. **Sensitivity Analyses***

Variable	Lifestyle Intervention vs. Placebo Intervention			Metformin Intervention vs. Placebo Intervention		
	Δ Cost, $	Δ QALY	Δ Cost/Δ QALY, $	Δ Cost, $	Δ QALY	Δ Cost/Δ QALY, $
Base-case analysis	635	0.57	1124	3922	0.13	31 286
Age 25–44 y	−395	0.63	Cost-saving	2574	0.27	9573
Age 45–54 y	489	0.63	781	4024	0.13	30 013
Age 55–64 y	1807	0.53	3409	4413	0.07	64 904
Age 65–74 y	2617	0.39	6646	4119	0.02	173 593
Age ≥ 75 y	2508	0.21	11 700	3255	0.01	273 207
Reduced cost†	−3696	0.57	Cost-saving	220	0.13	1755
20% reduced effectiveness	1417	0.46	3102	4084	0.11	38 145
50% reduced effectiveness	2371	0.30	7886	4307	0.80	52 562
Reduced cost† and 20% reduced effectiveness	−2181	0.41	Cost-saving	635	0.10	6576
Reduced cost† and 50% reduced effectiveness	−348	0.23	Cost-saving	1198	0.06	20 994
0% discount rate	−1526	0.99	Cost-saving	4041	0.24	17 110
5% discount rate	1382	0.42	3271	3784	0.09	42 686
Societal perspective	4967	0.57	8790	3748	0.13	29 900

* QALY = quality-adjusted life-year.
† Assumes that lifestyle intervention is implemented in a closed group of 10 patients and that metformin intervention is implemented with generic metformin.

interventions relative to the placebo intervention over a lifetime.

In these analyses, we used a previously developed and published simulation model (11). We modified this simulation model to include progression from impaired glucose tolerance to diabetes, recognize the 10-year delay between the onset and clinical diagnosis of type 2 diabetes, incorporate new data describing costs and health utility scores, and incorporate the most recently published data from the UKPDS on the development and progression of complications among intensively treated patients with type 2 diabetes.

Compared with the placebo intervention, the lifestyle and metformin interventions produced clinically meaningful reductions in type 2 diabetes and its microvascular, neuropathic, and cardiovascular complications. Our projections presented in the **Figure** indicate that the lifestyle and metformin interventions can delay and prevent type 2 diabetes by forestalling its onset by several years and reducing its cumulative incidence.

From the perspective of a health system, the lifestyle intervention was highly cost-effective, costing only $1100 per QALY, and the metformin intervention was in a generally cost-effective range, costing approximately $31 300 per QALY. The lifestyle intervention, compared with the metformin intervention, cost less and resulted in better health outcomes. In sensitivity analysis, we observed important differences by age. Whereas the lifestyle intervention was cost-saving in participants younger than 45 years of age and was cost-effective even in the oldest age groups, the metformin intervention was not cost-effective in participants older than 65 years of age. Otherwise, the results were robust to plausible changes in implementation strategy and participant adherence, as manifest by changes in both costs and treatment effectiveness. Under a scenario of both reduced costs and 20% to 50% reduced effectiveness, the lifestyle intervention was cost-saving relative to the placebo intervention and the metformin intervention cost only $6600 to $21 000 per QALY.

Many recent studies have assessed the relative cost-effectiveness of interventions in diabetes. Few interventions in diabetes are cost-saving, that is, the experimental intervention is both more effective and less expensive than the comparator. Cost-saving interventions in diabetes include preconception counseling for women with type 1 diabetes (30), angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker therapy for patients with clinical nephropathy (31, 32), and intensive blood pressure control for patients with hypertension (33). A recent report estimated that intensive glycemic control for patients with newly diagnosed type 2 diabetes costs approximately $41 000 per QALY over a lifetime (11) and statin therapy in patients with type 2 diabetes, no coronary disease, and total cholesterol levels greater than 5.18 mmol/L (>200 mg/dL) costs approximately $52 000 per QALY (11).

Cost-saving interventions present no difficulty with respect to policy implications. They should be rapidly and widely implemented since they are more effective and less expensive than existing therapies. However, most new treatments in diabetes are more effective and costly, requiring incremental resources per QALY. There is no universally accepted rule to evaluate such treatments (34). Laupacis and colleagues (35) have proposed a system to rate interventions on the basis of the likely magnitude of the net benefit associated with their application (cost per QALY). They argue that interventions that cost less than $20 000 per QALY are an appropriate way to use resources and those that cost $20 000 to $100 000 per QALY are probably appropriate, but those that cost greater than $100 000 per QALY may not be a good use of resources.

We based our model on the DPP. No simulation model can perfectly represent reality, and all models have inherent limitations (36). Participants in the DPP, while broadly representative of the population with impaired glucose tolerance, were volunteers and may have been more highly motivated than nonparticipants. The DPP could not study all clinical relevant interventions or measure disease progression and intervention effects over a lifetime. When long-term information is not available, models may be used to integrate evidence from clinical trials to make inferences about future economic, quality of life, and health outcomes and to provide data for decision making. The predictions provided by a model depend on the clinical trial itself and the assumptions made in the simulation. In our base-case analyses, we assumed that the DPP interventions were applied as they were in the DPP for as long as an individual remained nondiabetic. We further assumed that the costs were the same as those in the DPP, the interventions would remain as effective as they were in the DPP, and participants developing diabetes would receive intensive therapy. Higher costs or lower effectiveness of interventions for diabetes prevention would tend to reduce the cost-effectiveness of diabetes prevention.

In summary, compared with the placebo intervention, the DPP lifestyle and metformin interventions provided substantial health benefits at an attractive cost. The lifestyle intervention, compared with the metformin intervention, provided greater health benefits at lower costs and, from the perspective of a fiscally prudent policymaker, represents the intervention of choice. Investment in DPP lifestyle and metformin interventions in high-risk individuals with impaired glucose tolerance may help stem the current epidemic of diabetes.

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Appendix Table 1. **Guidelines for Distributions around Variables without Published Variability Data in Probabilistic Sensitivity Analysis***

Variable Types	Distribution	Decreased Variation, %	Increased Variation, %
Small costs (<$300)	Triangular	0.25	0.25
Large costs	Logistic normal	0.15	NA
Probabilities and hazard rates	Logistic normal	0.25	NA
Discounts	Triangular	0.3333333	0.6666667

* NA = not applicable.

Appendix: Parameter Values for Base-Case Analysis and Distributions Applied in Probabilistic Sensitivity Analysis

Appendix Tables 1 to 7 include the parameter values used in the diabetes screening and disease progression model. We applied values in the "Base-Case Analysis" columns in all model runs unless otherwise specified (in 1-way and probabilistic sensitivity analyses). The "Probabilistic Sensitivity Analysis Distribution" columns list the distributions from which we randomly sampled parameter values in the probabilistic sensitivity analyses. We report CIs for those parameters for which CIs were available or could be calculated without any named distribution. Normal distributions based on those CIs were applied in the analysis. The ranges for parameters without published variability data followed the guidelines in **Appendix Table 1**. We applied relevant limits to all ranges (for example, quality of life and probabilities must be between 0 and 1).

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Collection and assembly of data: W.H. Herman, P. Zhang.

Appendix Table 2. **Variables Specific to Prediabetes or the Diabetes Prevention Program***

Variable	Value		Base Source (Author, Reference)	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Prediabetes				
Annual probability of onset of diabetes	0.108	Normal (0.089 to 0.127)	DPP data	–
Hazard rates				
Hypertension	0.0506	Normal (0.006 to 0.098)	DPP data	–
High cholesterol level	0.0375	Normal (0.000 to 0.084)	DPP data	–
Normal to microalbuminuria	0	Not varied	Assumed	–
Normal to peripheral neuropathy	0	Not varied	Assumed	–
CHD risk factor, UKPDS	0.58	Normal (0.54 to 0.62)	Qureshi et al., 14	Calculated by using logit transforms; reported SEs
Stroke risk factor, UKPDS	0.56	Normal (0.50 to 0.63)	Qureshi et al., 14	Calculated by using logit transforms; reported SEs
DPP				
Cost of oral glucose tolerance test	17.80	Triangular (13.35 to 22.25, 17.80)	HCFA, 37	Assumed
Diabetes onset risk reduction				
Metformin				
Years 1–3	29.9	Normal (16 to 41)	DPP data	Reported CI
Years 4–95	29.9	Normal (16 to 41)	Assumed	Assumed
Lifestyle				
Years 1–95	55.3	Normal (45 to 63)	DPP data	Reported CI
Years 4–95	55.3	Normal (45 to 63)	Assumed	Assumed
Hypertension onset risk reduction				
Metformin				
Years 1–3	0	Not varied	DPP data	–
Years 4–95	0	Not varied	Assumed	–
Lifestyle				
Years 1–3	100	Not varied	DPP data	–
Years 4–95	100	Not varied	Assumed	–
High cholesterol onset risk reduction				
Metformin, years 1–95	0	Not varied	DPP data	–
Lifestyle				
Years 1–3	22.6	Log. normal (22.6, 16.95)	DPP data	Assumed
Years 4–95	22.6	Log. normal (22.6, 16.95)	Assumed	Assumed
Intervention cost, $				
Placebo				
Year 1	43	Triangular (32 to 43, 54)	Herman et al., 7	Assumed
Years 2–3	18	Triangular (14 to 18, 23)	Herman et al., 7	Assumed
Years 4–95	18	Triangular (14 to 18, 23)	Assumed	Assumed
Metformin				
Year 1	1019	Log. normal (1019, 866)	Herman et al., 7	Assumed
Year 2	772	Log. normal (772, 656)	Herman et al., 7	Assumed
Year 3	751	Log. normal (751, 638)	Herman et al., 7	Assumed
Years 4–95	751	Log. normal (751, 638)	Assumed	Assumed
Lifestyle				
Year 1	1399	Log. normal (1399, 1189)	Herman et al., 7	Assumed
Year 2	679	Log. normal (679, 577)	Herman et al., 7	Assumed
Year 3	702	Log. normal (702, 597)	Herman et al., 7	Assumed
Years 4–95	702	Log. normal (702, 597)	Assumed	Assumed
Impact of intervention on medical costs, $				
Placebo				
Women, years 1–3	53	Log. normal (53, 45)	Herman et al., 7	Assumed
Women, years 4–95	0	Not varied	Assumed	–
Men, years 1–3	23	Log. normal (23, 20)	Herman et al., 7	Assumed
Men, years 4–95	0	Not varied	Assumed	–
Metformin				
Women, years 1–3	−20	Log. normal (−20, −17)	Herman et al., 7	Assumed
Women, years 4–95	0	Not varied	Assumed	–
Men, years 1–3	83	Log. normal (83, 71)	Herman et al., 7	Assumed
Men, years 4–95	0	Not varied	Assumed	–
Lifestyle				
Women, years 1–3	−33	Log. normal (−33, −28)	Herman et al., 7	Assumed
Women, years 4–95	0	Not varied	Assumed	–
Men, years 1–3	−105	Log. normal (−105, −89)	Herman et al., 7	Assumed
Men, years 4–95	0	Not varied	Assumed	–

* CHD = coronary heart disease; DPP = Diabetes Prevention Program; HCFA = Health Care Financing Administration; UKPDS = United Kingdom Prospective Diabetes Study.
† Log. normal (*a*, *b*) = logistic normal distribution (mean, lower bound); normal (*a* to *b*) = normal distribution (95% CI); triangular (*a* to *b*, *c*) = triangular distribution (minimum to maximum, mode).

Appendix Table 3. **Variables Specific to Coffey and Colleagues' Additive Quality-of-Life Model***

Variable	Value		Base Source (Author, Reference)	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Intercepts				
Diabetes	0.6890	Normal (0.662 to 0.716)	Coffey et al., 26	Based on reported SEs
Prediabetes	0.7302	Normal (0.713 to 0.748)	DPP data	Calculated based on reported SEs for base model intercept and coefficients associated with BMI < 30 kg/m^2 and male sex
Coefficients associated with characteristics				
Women	−0.0380	Normal (−0.052 to −0.024)	Coffey et al., 26	Based on reported SEs
Hypertension	−0.0110	Normal (−0.025 to 0.003)	Coffey et al., 26	Based on reported SEs
Blindness	−0.1700	Normal (−0.192 to −0.148)	Coffey et al., 26	Based on reported SEs
Nephropathy	−0.0110	Normal (−0.029 to 0.007)	Coffey et al., 26	Based on reported SEs
End-stage renal disease	−0.0780	Normal (−0.129 to −0.027)	Coffey et al., 26	Based on reported SEs
Peripheral neuropathy	−0.0650	Normal (−0.081 to −0.049)	Coffey et al., 26	Based on reported SEs
Foot ulcer	−0.0990	Normal (−0.124 to −0.074)	Coffey et al., 26	Based on reported SEs
Lower-extremity amputation	−0.1050	Normal (−0.144 to −0.066)	Coffey et al., 26	Based on reported SEs
History of cardiac arrest or myocardial infarction	−0.0520	Normal (−0.074 to −0.030)	Coffey et al., 26	Based on reported SEs
Stroke	−0.0720	Normal (−0.103 to −0.041)	Coffey et al., 26	Based on reported SEs
DPP lifestyle intervention	0.0189	Normal (0.012 to 0.026)	DPP data	Based on reported SEs
DPP drug intervention	0.0031	Normal (−0.004 to 0.010)	DPP data	Based on reported SEs
BMI ≥ 30.0 kg/m^2	−0.0210	Normal (−0.035 to −0.007)	Coffey et al., 26	Based on reported SEs

* BMI = body mass index; DPP = Diabetes Prevention Program.
† Normal (*a* to *b*) = normal distribution (95% CI).

Appendix Table 4. **Variables Specific to Brandle and Colleagues' Multiplicative Cost Model***

Variable	Value		Base Source (Author, Reference)	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Diabetes costs				
Base	$1684	Not varied	Brandle et al., 25	–
Multiplier				
Female	1.2500	Normal (1.112 to 1.394)	Brandle et al., 25	Based on reported SEs
White	1.0000	Not varied	Assumed	–
African American	0.8200	Normal (0.694 to 0.96)	Brandle et al., 25	Based on reported SEs
Hispanic	1.0000	Not varied	Assumed	–
Asian	1.0000	Not varied	Assumed	–
Native American	1.0000	Not varied	Assumed	–
BMI ≥ 30 kg/m^2	1.0100	Normal (1.001 to 1.019)	Brandle et al., 25	Based on reported SEs
Oral antidiabetic agents	1.1000	Normal (0.852 to 1.412)	Brandle et al., 25	Based on reported SEs
Insulin	1.5900	Normal (1.221 to 2.061)		Based on reported SEs
Microalbuminuria	1.1700	Normal (0.941 to 1.451)	Brandle et al., 25	Based on reported SEs
Nephropathy	1.3000	Normal (1.103 to 1.526)	Brandle et al., 25	Based on reported SEs
End-stage renal disease with dialysis	10.5300	Normal (4.612 to 24.059)	Brandle et al., 25	Based on reported SEs
History of stroke	1.3000	Normal (1.107 to 1.519)	Brandle et al., 25	Based on reported SEs
Angina	1.7300	Normal (1.316 to 2.282)	Brandle et al., 25	Based on reported SEs
History of cardiac arrest or myocardial infarction	1.9000	Normal (1.663 to 2.16)	Brandle et al., 25	Based on reported SEs
Peripheral vascular disease	1.3100	Normal (1.15 to 1.481)	Brandle et al., 25	Based on reported SEs
Hypertension (treated)	1.2400	Normal (1.089 to 1.402)	Brandle et al., 25	Based on reported SEs
Prediabetes costs				
Base	$1296	Not varied	DPP data	–
Multiplier				
Female	1.1420	Normal (1.02 to 1.278)	DPP data	Assumed same relative variance as for diabetes
White	1.0000	Not varied	Assumed	–
African American	0.8200	Normal (0.694 to 0.96)	Assumed same as diabetes	Based on reported SE
Hispanic	1.0000	Not varied	Assumed	–
Asian	1.0000	Not varied	Assumed	–
Native American	1.0000	Not varied	Assumed	–
BMI ≥ 30 kg/m^2	1.0100	Normal (1.001 to 1.019)	Assumed same as diabetes	Assumed same as diabetes
Oral antidiabetic agents	1.0000	Not varied	Assumed	–
Insulin	1.0000	Not varied	Assumed	–
Microalbuminuria	1.0000	Not varied	Assumed	–
Nephropathy	1.0000	Not varied	Assumed	–
End-stage renal disease with dialysis	1.0000	Not varied	Assumed	–
History of stroke	1.3000	Normal (1.107 to 1.519)	Assumed same as diabetes	Assumed same as diabetes
Angina	1.7300	Normal (1.316 to 2.282)	Assumed same as diabetes	Assumed same as diabetes
History of cardiac arrest or myocardial infarction	1.9000	Normal (1.663 to 2.16)	Assumed same as diabetes	Assumed same as diabetes
Peripheral vascular disease	1.0000	Normal (1.15 to 1.481)	Assumed same as diabetes	Assumed same as diabetes
Hypertension (treated)	1.2400	Normal (1.089 to 1.402	Assumed same as diabetes	Assumed same as diabetes
Acute event costs				
Acute myocardial infarction	$24 500	Normal ($15 000 to $50 000)	Brandle et al., 25	Reported IQR
Stroke	$26 600	Normal ($15 400 to $44 900)	Brandle et al., 25	Reported IQR
Lower-extremity amputation	$37 600	Normal ($23 300 to $62 200)	Brandle et al., 25	Reported IQR
Other				
BMI	30	Not varied	Assumed	–
Peripheral vascular disease prevalence	39	Normal (36.4 to 41.6)	Brandle et al., 25	Calculated using binomial distribution

* BMI = body mass index; DPP = Diabetes Prevention Program; IQR = interquartile range.
† Normal (*a* to *b*) = normal distribution (95% CI).

Appendix Table 5. **Discount Rate Variables***

Variable	Value		Base Source	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Discount rate applied to costs	3.00	Triangular (2.00 to 5.00, 3.33)	Assumed	Assumed
Discount rate applied to QALYs	3.00	Triangular (2.00 to 5.00, 3.33)	Assumed	Assumed

* QALY = quality-adjusted life-year.
† Triangular (*a* to *b*, *c*) = triangular distribution (minimum to maximum, mode).

Appendix Table 6. **Variables Specific to Disease Progression***

Variable	Value		Base Source (Author, Reference)	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Nephropathy hazard rates				
Normal to microalbuminuria				
Baseline	0.0202	Normal (0.0192 to 0.0222)	Adler et al., 20	Based on reported CIs
Hypertension with moderate control	0.0202	Normal (0.0192 to 0.0222)	Adler et al., 20	Based on reported CIs
Microalbuminuria to nephropathy				
Baseline	0.0284	Normal (0.0253 to 0.0325)	Adler et al., 20	Based on reported CIs
Hypertension with moderate control	0.0284	Normal (0.0253 to 0.0325)	Adler et al., 20	Based on reported CIs
Nephropathy to end-stage renal disease				
Baseline	0.02327	Normal (0.0151 to 0.0305)	Adler et al., 20	Based on reported CIs
Hypertension with moderate control	0.02327	Normal (0.0151 to 0.0305)	Adler et al., 20	Based on reported CIs
Neuropathy hazard rates				
Normal to peripheral neuropathy	0.036	Log. normal (0.036, 0.027)	DCCTRG, 38	Assumed
Peripheral neuropathy to lower-extremity amputation	0.0067	Log. normal (0.028, 0.021)	UKPDS 38, 23	Assumed
Probability of additional amputations, %	11	Log. normal (11, 8)	Reiber et al., 39	Assumed
Probability of diabetes foot ulcer, %	4.00	Log. normal (4.00, 3.00)	Reiber et al., 39; Moss et al., 40	Assumed
Probability of death from amputation, %	10.5	Log. normal (10.5, 8)	Reiber et al., 39	Assumed
Retinopathy hazard rates				
Normal to photocoagulation				
Baseline	0.011	Log. normal (0.011, 0.008)	DCCTRG, 38	Assumed
Hypertensive with moderate control	0.0166	Log. normal (0.017, 0.012)	UKPDS 33, 13	Assumed
Photocoagulation to blindness				
Baseline	0.1065	Log. normal (0.107, 0.080)	UKPDS 33, 13	Assumed
Hypertensive with moderate control	0.1065	Log. normal (0.107, 0.080)	UKPDS 33, 13	Assumed
Cardiovascular heart disease hazard rates				
None			–	–
Stroke hazard rates				
Stroke to death				
Immediate	0.142	Log. normal (0.142, 0.107)	Sacco et al., 41	Assumed
1 y	0.092	Log. normal (0.092, 0.069)	Sacco et al., 41	Assumed

* DCCTRG = Diabetes Control and Complications Trial Research Group; UKPDS = United Kingdom Prospective Diabetes Study.
† Log. normal (*a*, *b*) = logistic normal distribution (mean, lower bound); normal (*a* to *b*) = normal distribution (95% CI).

Appendix Table 7. **Variables Specific to Moderate Hypertension Control***

Variable	Value		Base Source (Author, Reference)	Distribution Notes
	Base-Case Analysis	Probabilistic Sensitivity Analysis Distribution†		
Treatment effect, %				
Relative risk reduction of CHD	13	Log. normal (13, 10)	UKPDS 38, 23	Assumed
Relative risk reduction of stroke	17	Not varied	UKPDS 38, 23	–

* CHD = cardiovascular heart disease; UKPDS = United Kingdom Prospective Diabetes Study.
† Log. normal (*a*, *b*) = logistic normal distribution (mean, lower bound).